IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I, Peter Offord declare

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland, residing at Chapel Mill Cottage, Lenham Heath Road, Lenham, Kent, ME17 2BJ, United Kingdom.

2. That I am well acquainted with the English and Chinese languages.

3. That the attached is a true translation into the English language of the certified copy of Chinese Patent Application No. 02153819.0 filed on 28th November 2002.

4. That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the patent application in the United States of America or any patent issuing thereon.

DECLARED THIS 21st DAY OF FEBRUARY 2005

Peter Offord

Certificate

It is hereby certified that the attachment is a copy of the following Patent Application filed with this Office:

Date of Filing: 28/11/2002

Application No.: 02 1 53819.0

Category of Application: invention

Name of invention: Sinomenine and sinomenine compounds, synthesis and applications

Applicants: SHANGHAI INSTITUTE OF MATERIA MEDICA, Chinese Academy of Sciences; LES LABORATOIRES SERVIER

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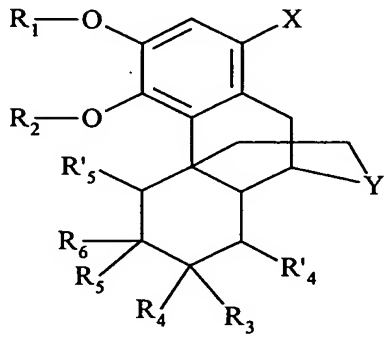
07/08/2003

Wang Jingchuan.

The Director of the State Intellectual Property Office
People's Republic of China

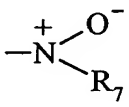
Claims

1. Compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases,



(I),

within which,

- R_1 represents an alkyl group,
- R_2 represents a hydrogen atom or an alkylcarbonyl group,
- Y represents a group NR_7 or  wherein R_7 represents an alkyl group,
- R_3 represents a hydroxy or alkoxy group,
- R_4 and R'_4 each represent a hydrogen atom or together form an additional bond, or R_3 and R_4 together form an oxo or $=N\text{-}OR_8$ group wherein R_8 represents a hydrogen atom or an alkyl group,
- R_6 represents a hydroxy group, an alkylcarbonyloxy group wherein alkyl may be substituted by hydroxy, alkoxy, carboxyl or by alkoxycarbonyl, or an alkoxy group,
- R_5 and R'_5 each represent a hydrogen atom or together form an additional bond, or R_5 and R_6 together form an oxo, $=N\text{-}OR_9$ or $=N\text{-}NR_{10}R_{11}$ group, where R_9, R_{10}, and R_{11} may be identical or may differ whilst each is a hydrogen atom or an alkyl group,
- in addition X represents a halogen atom,

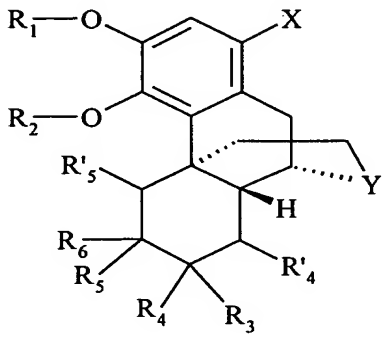
with the proviso that the compound of formula (I) cannot represent 1-bromo-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one,

and wherein it should be understood that

- 'alkyl' here refers to an alkyl group containing between 1 and 6 carbon atoms, which may be linear or branched,
- 'alkoxy' here refers to an alkoxy group containing between 1 and 6 carbon atoms, which may be linear or branched.

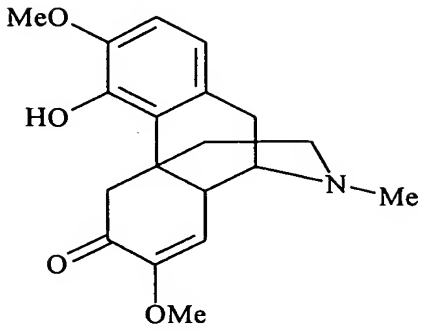
2. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1, wherein R_1 represents a methyl group.
3. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1, wherein R_2 represents a hydrogen atom.
4. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1, wherein R_2 represents a carboxylhydroxy group.
5. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1, wherein R_2 represents an ethylhydroxy group.
6. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1, wherein Y represents group NR_7.
7. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1, wherein X represents a chlorine atom.
8. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1, wherein X represents a bromine atom.
9. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1, wherein R_3 represents an alkoxy group and R_4 and R'_4 form an additional bond.

10. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1, wherein R_5 represents a hydrogen atom.
11. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1, wherein R_6 represents an OH group.
12. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1, wherein R_6 represents an alkylcarbonyloxy group.
13. The compounds of formula (I) as set down in Claim 1, including (9α,13α)-1-chloro-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4,6-diol.
14. The compounds of formula (I) as set down in Claim 1, including (9α,13α)-1-chloro-3,7-dimethoxy-17-methyl-4-(propionyloxy)-7,8-didehydromorphinan-6-yl propionate.
15. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1, that have the configuration shown by the following formula (I'):



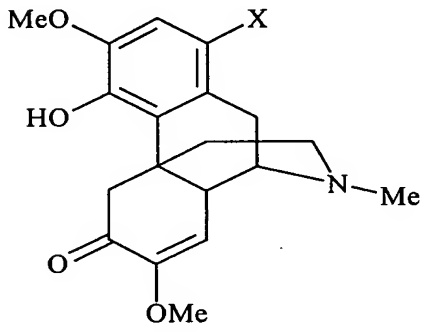
(I')

16. A process for preparation of the compounds of formula (I) set down in Claim 1, characterised in that the compound of formula (II) is used as starting material:



(II),

the aforementioned compound of formula (II) being obtained by extraction from the stem of *Sinomenium acutum*;
the compound of formula (II) is subjected to the action of a halogenating agent such as SO_2Cl_2 or Br_2, to obtain the compound of formula (I/a), a particular case of the compounds of formula (I):

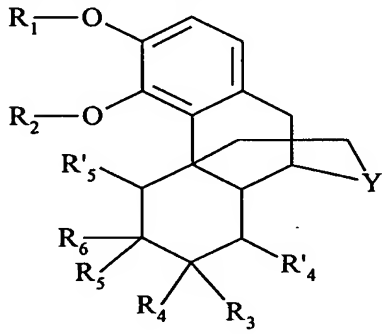


(I/a),

wherein the definition of X is the same as in formula (I), the compound of formula (I/a) may be subjected to a routine chemical reaction to obtain the compound with the complete formula (I), this may be purified with conventional separation techniques and may be transformed at a suitable time into a salt with the addition of pharmaceutically acceptable acids or bases, in addition it may be converted into its isomer by conventional separation if required.

17. Pharmaceutical compositions, consisting of at least one type of compound of formula (I) as set down in any of Claims 1 - 15, or its addition salt with a pharmaceutically acceptable acid or base, in addition to one or more types of pharmaceutical excipient.

18. Pharmaceutical compositions set down in Claim 17 for use in the preparation of drugs for the purpose of treatment of memory impairment associated with cerebral ageing, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease and frontal lobe and cortical dementias.
19. The use of sinomenine and/or sinomenine compounds in the preparation of pharmaceutical compositions for the purpose of treatment of memory impairment associated with cerebral ageing, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease and frontal lobe and cortical dementias.
20. The use of sinomenine, as set down in Claim 19, in the preparation of pharmaceutical compositions for the treatment of memory impairment associated with cerebral ageing, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease and frontal lobe and cortical dementias.
21. The use of sinomenine compounds, as set down in Claim 19, in the preparation of pharmaceutical compositions for the treatment of memory impairment associated with cerebral ageing, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease and frontal lobe and cortical dementias.
22. The use of sinomenine compounds, of formula (Ia), as set down in Claim 19, in the preparation of pharmaceutical compositions for the treatment of memory impairment associated with cerebral ageing, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease and frontal lobe and cortical dementias with the following structure:



(Ia),

wherein R_1, R_2, R_3, R_4, R'_4, R_5, R'_5, R_6 and Y are as hereinbefore defined as set down in Claim 1.

23. The use of the sinomenine compounds: (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one hydrazone; (7α,9α,13α)-4-hydroxy-3,7-dimethoxy-17-methylmorphinan-6-one; (7β,9α,13α)-4-hydroxy-3,7-dimethoxy-17-methylmorphinan-6-one; (9α,13α)-3,7-dimethoxy-17-methyl-6-oxo-7,8-didehydromorphinan-4-yl propionate; (9α,13α)-3,4,7-trimethoxy-17-methyl-7,8-didehydromorphinan-6-one; (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one oxime; (9α,13α)-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4,6-diol; (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one N-oxide; (9α,13α)-6-amino-3,7-dimethoxy-17-methylmorphinan-4-ol; 4-{[(9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-yl]oxy}-4-oxobutanoic acid; (9α,13α)-3,7-dimethoxy-17-methyl-4-(propionyloxy)-7,8-didehydromorphinan-6-yl propionate, as set down in Claim 19, in the preparation of pharmaceutical compositions for the treatment of memory impairment associated with cerebral ageing, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease and frontal lobe and cortical dementias.
24. The use of pharmaceutical compositions, including sinomenine or sinomenine compounds, in addition to one or more types of medicinal excipient, for the treatment of memory impairment associated with cerebral ageing, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease and frontal lobe and cortical dementias.

Description

Sinomenine and sinomenine compounds, synthesis and applications

Sinomenium acutum is a plant taking the form of a ligneous liana which is widespread in the centre, South-East and South-West of China and is included in the Chinese Pharmacopoeia (People's Republic of China Pharmacopoeia Committee, 2000). It contains high levels of alkaloids of varied chemical structure, such as sinomenine, sinoacutine, ethylsinomenine, disinomenine, tetrahydroepiberberine, tuduranine and magnoflorine (pp.1156-1160, Huang Tai-Kang, Handbook of the Composition and Pharmacology of Common Chinese Drugs, Chinese Medical Science and Technology Publishing House, Beijing, 1994).

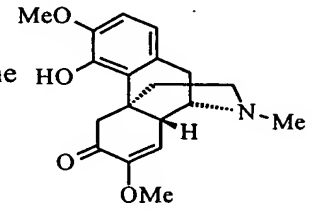
Sinomenine is a morphine-like alkaloid and is the main constituent of this plant and extensive research has already been conducted into this chemical; of particular importance in this respect has been the likelihood of this drug exhibiting anti-inflammatory, immunosuppressive, anti-arrhythmic and analgesic properties (Qiang Liu *et al.*, Chinese Traditional and Herbal Drugs, 1997, 28 (4), 247).

We have now discovered from animal test models that sinomenine has memory/cognition facilitating properties.

Ageing of the population due to increased life expectancy has brought with it a major increase in cognitive disorders associated with normal cerebral ageing or associated with pathological cerebral ageing occurring in the courses of neurodegenerative diseases (for example Alzheimer's disease).

The majority of substances used today in treating cognitive disorders associated with ageing act by facilitating the central cholinergic systems – either directly, as in the case of acetylcholinesterase inhibitors (tacrine, donepezil) and cholinergic agonists (nefiracetam), or indirectly, as in the case of nootropic agents (piracetam, pramiracetam) and cerebral vasodilators (vinpocetine).

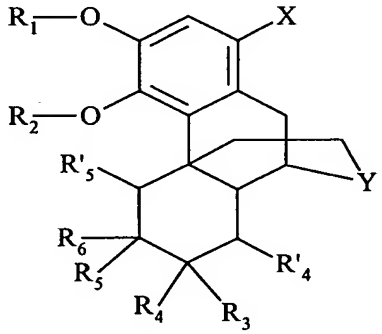
Therefore, synthesis of new compounds that are capable of opposing the cognitive disorders associated with ageing and/or of improving cognitive processes is of great importance.

The present invention relates, on the one hand, to the use of sinomenine 

and/or sinomenine compounds in memory/cognition disorders and, on the other hand, to the synthesis of new compounds, especially those with pharmacological properties of value to the same field.

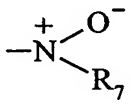
Diagram 1 is a flow chart of the extraction process of the compound of formula (II), used as raw material in this invention.

The present invention relates more specifically to compounds of formula (I) :



(I),

within which,

- R_1 represents an alkyl group,
- R_2 represents a hydrogen atom or an alkylcarbonyl group,
- Y represents a group NR_7 or 

wherein R_7 represents an alkyl group,
- R_3 represents a hydroxy or alkoxy group,

- R_4 and R'_4 each represent a hydrogen atom or together form an additional bond, or R_3 and R_4 together form an oxo or =N-OR_8 group wherein R_8 represents a hydrogen atom or an alkyl group,
- R_6 represents a hydroxy group, an alkylcarbonyloxy group wherein alkyl may be substituted by hydroxy, alkoxy, carboxyl or by alkoxycarbonyl, or an alkoxy group,
- R_5 and R'_5 each represent a hydrogen atom or together form an additional bond, or R_5 and R_6 together form an oxo, =N-OR_9 or =N-$NR_{10}R_{11}$ group, where R_9, R_{10}, and R_{11} may be identical or may differ whilst each is a hydrogen atom or an alkyl group,
- in addition X represents a halogen atom,

with the proviso that the compound of formula (I) cannot represent 1-bromo-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one,

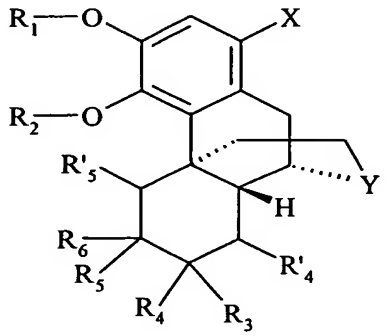
- 'alkyl' here refers to an alkyl group containing between 1 and 6 carbon atoms, which may be linear or branched,
- 'alkoxy' here refers to an alkoxy group containing between 1 and 6 carbon atoms, which may be linear or branched,

and includes any enantiomer or diastereoisomer, and their addition salts formed by the addition of a compound of formula (I) to any pharmaceutically acceptable acids or bases.

Without imposing any limitation, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphonic acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, methanesulphonic acid, camphoric acid, oxalic acid may be mentioned as pharmaceutically acceptable acids.

Without imposing any limitation, sodium hydroxide, potassium hydroxide, triethylamine, tert-butylamine etc. may be mentioned as pharmaceutically acceptable bases.

The preferred configuration of compounds of formula (I) claimed for the invention is shown by formula (I'):



(I')

Preferably group R_1 represents a methyl group.

Advantageously, R_2 represents a hydrogen atom or a group EtCO.

Y represents, preferably, group a NR_7 and, even more preferably, a group N-Me.

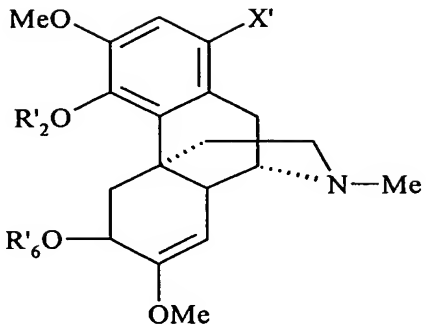
X represents, very preferably, a chlorine or bromine atom.

Advantageously, this invention relates to compounds of formula (I), and of these R_3 represents an alkoxy group and R_4 and R'_4 together form an additional bond.

Preferably R_5 represents a hydrogen atom.

R_6 represents, advantageously, an OH or alkylcarbonyloxy group and, more especially, ethylcarbonyloxy.

Very preferably, the invention relates to compounds of formula (I''):



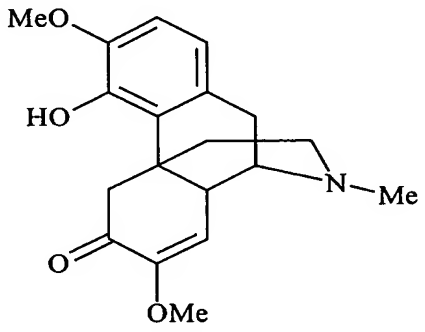
(I")

wherein R'_2 and R'_6, which may be the same or different, represent a hydrogen atom or an alkylcarbonyl group and X' represents a chlorine or bromine atom.

Even more preferably, the invention relates to the following compounds of formula (I), (9α,13α)-1-chloro-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4,6-diol and (9α,13α)-1-chloro-3,7-dimethoxy-17-methyl-4-(propionyloxy)-7,8-didehydromorphinan-6-yl propionate.

The enantiomers and diastereoisomers of the preferred compounds to which this invention relates, and their addition salts with pharmaceutically acceptable acids or bases, thus form an integral part of the invention.

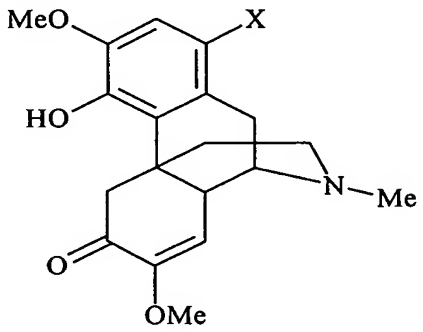
This invention further relates to a method of preparation of compounds of formula (I), a process, characterised in that a compound of formula (II) is used as starting material:



(II),

wherein the compound of formula (II) is obtained by extraction from the stem of *Sinomenium acutum* according to the appended diagram 1;

the compound of formula (II) is subjected to the action of a halogenating agent such as SO_2Cl_2 or Br_2, to obtain the compound of formula (I/a), a particular case of the compounds of formula (I):



(I/a),

wherein the definition of X is the same as in formula (I), the compound of formula (I/a) may be subjected to a routine chemical reaction to obtain the compound with the complete formula (I), this may be purified with conventional separation techniques and may be transformed at a suitable time into a salt with the addition of pharmaceutically acceptable acids or bases, in addition it may be converted into its isomer by conventional separation if required.

Apart from the fact that the compounds presented by this invention are new, they also possess properties of facilitating cognitive processes, allowing their use in the treatment of cognitive deficiencies associated with cerebral ageing and neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease, and frontal lobe and subcortical dementias.

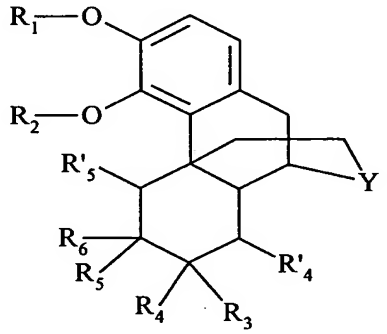
This invention also relates to pharmaceutical compositions consisting of active ingredients comprising at least one compound of formula (I) together with one or more appropriate, inert, non-toxic excipients.

In addition, the applicant has discovered that sinomenine and/or sinomenine compounds possess memory/cognition facilitating properties.

Therefore, this invention relates also to the use of sinomenine and/or sinomenine compounds in the preparation of pharmaceutical compositions for use in the treatment of

cognitive deficiencies associated with cerebral ageing and with neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease, and frontal lobe and subcortical dementias.

More specifically, this invention relates to the use of sinomenine and/or sinomenine compounds, such as those of formula (1a), in the preparation of pharmaceutical compositions for the treatment of memory impairment associated with cerebral ageing, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease and frontal lobe and cortical dementias, wherein formula (Ia) of these compounds is as follows:



(Ia),

wherein R_1, R_2, R_3, R_4, R'_4, R_5, R'_5, R_6 and Y are as hereinbefore defined in formula (I), and where the compounds referred to are more specifically (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one hydrazone; (7α,9α,13α)-4-hydroxy-3,7-dimethoxy-17-methylmorphinan-6-one; (7β,9α,13α)-4-hydroxy-3,7-dimethoxy-17-methylmorphinan-6-one; (9α,13α)-3,7-dimethoxy-17-methyl-6-oxo-7,8-didehydromorphinan-4-yl propionate; (9α,13α)-3,4,7-trimethoxy-17-methyl-7,8-didehydromorphinan-6-one; (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one oxime; (9α,13α)-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4,6-diol; (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one N-oxide; (9α,13α)-6-amino-3,7-dimethoxy-17-methylmorphinan-4-ol; 4-{[(9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-yl]-oxy}-4-oxobutanoic acid; (9α,13α)-3,7-dimethoxy-17-methyl-4-(propionyloxy)-7,8-didehydromorphinan-6-yl propionate.

One of the benefits of this invention relates to the use of sinomenine in the preparation of pharmaceutical compositions for use in the treatment of cognitive deficiencies associated with cerebral ageing and with neurodegenerative diseases.

Another particularly important aspect of this invention relates to the use of compounds of formula (Ia), in the preparation of pharmaceutical compositions for use in treatment of cognitive deficiencies associated with cerebral ageing and with neurodegenerative diseases, particularly such compounds of formula (Ia) as (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one hydrazone; (7α,9α,13α)-4-hydroxy-3,7-dimethoxy-17-methylmorphinan-6-one; of (7β,9α,13α)-4-hydroxy-3,7-dimethoxy-17-methylmorphinan-6-one; (9α,13α)-3,7-dimethoxy-17-methyl-6-oxo-7,8-didehydromorphinan-4-yl propionate; (9α,13α)-3,4,7-trimethoxy-17-methyl-7,8-didehydromorphinan-6-one; (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one oxime; (9α,13α)-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4,6-diol; (9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one N-oxide; (9α,13α)-6-amino-3,7-dimethoxy-17-methylmorphinan-4-ol; 4-{[(9α,13α)-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-yl]oxy}-4-oxobutanoic acid; (9α,13α)-3,7-dimethoxy-17-methyl-4-(propionyloxy)-7,8-didehydromorphinan-6-yl propionate.

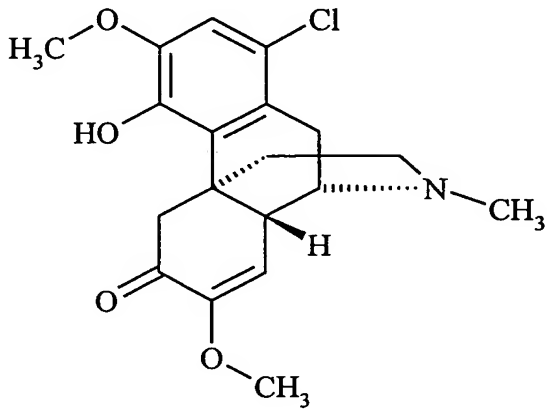
This invention also relates to the use of pharmaceutical compositions comprising sinomenine or its compounds, in combination with one or more pharmaceutically acceptable excipients, in the treatment of cognitive deficiencies associated with cerebral ageing and with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's disease, and frontal lobe and subcortical dementias.

In particular, the pharmaceutical compositions which may be prepared according to this invention are particularly suited to oral, parenteral (intravenous or subcutaneous) or nasal administration, and for usage in the preparation of tablets or dragées, sublingual tablets, gelatine capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations, drinkable suspensions etc..

Useful dosages may be varied according to the nature and severity of the disorder, the administration route and also the age and weight of the patient. Dosage varies from 0.01mg to 1g per day in one or more administrations.

The following implementations are for descriptive illustration of this invention, but should not be considered as limiting it in any way whatsoever.

Implementation Example 1: (9α,13α)-1-Chloro-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one



3 drops of SO_2Cl_2 are added to a solution of 5ml of $CHCl_3$ containing 100mg of a compound of formula (II). The reaction mixture is stirred at room temperature for 4 hours then pH adjusted to between 7 and 8 with $NaHCO_3$ solution; $CHCl_3$ is then used to carry out extraction. The organic phase is evaporated under reduced pressure and the residue obtained is chromatographed on silica gel using $CHCl_3$-MeOH (9 : 1) as eluant to yield the title compound in the form of a yellowish solid.

Melting point: 126-128°C

Implementation Example 2: (9α,13α)-1-Chloro-3,7-dimethoxy-17-methyl-6-oxo-8-didehydromorphinan-4-yl propionate

2ml of propionic anhydride are added slowly to a solution of 15ml of pyridine containing 100mg of the compound obtained in Implementation Example 1 and 100mg of DMAP, the reaction mixture is then stirred at room temperature for 3 hours and is then evaporated

and the residue obtained dissolved in a small volume of water. The solution obtained is adjusted to pH = 8-9 using $NaHCO_3$ solution and is then extracted with $CHCl_3$. The organic phase is washed 3 times with water, dried over sodium sulphate and evaporated. The residue obtained is chromatographed on silica gel using $CHCl_3$-MeOH (20 : 1) as eluant to yield the title compound in the form of a colourless oily matter.

Implementation Example 3: (6β,7β,9α,13α)-1-Chloro-3,7-dimethoxy-17-methylmorphinan-4,6-diol

720mg of the compound obtained in Implementation Example 1 are mixed with 100mg of PtO_2 and 50ml of anhydrous ethanol for 12 hours at room temperature under an H_2 atmosphere. Removing the PtO_2 using filtration, then removing the ethanol using vacuum evaporation, a syrupy residue is obtained. After washing the residue using 10ml of hot anhydrous ethanol, a powdery residue may be obtained by filtration collection, this may then be recrystallized in $CHCl_3/C_2H_5OH$, to obtain the title compound in white crystalline form.

Melting point: 210-212°C

Implementation Example 4: (9α,13α)-1-Chloro-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4,6-diol

500mg of $NaBH_4$ is added to a 15ml solution of methanol containing 500mg of the compound obtained in Implementation Example 1, and the reaction mixture stirred for 1.5 hours. The methanol is then evaporated off and the residue obtained extracted with $CHCl_3$. The organic phase is dried over Na_2SO_4 and evaporated under reduced pressure. The title compound is obtained in the form of white crystals, by recrystallization from Et_2O.

Melting point: 118-120°C

Implementation Example 5: (9α,13α)-1-Chloro-3,7-dimethoxy-17-methyl-4-(propionyloxy)-7,8-didehydromorphinan-6-yl propionate

The title compound is obtained using the method described in Implementation Example 2 and by using the compound obtained in Implementation Example 4.

Oily matter.

Implementation Example 6: (6β,7β,9α,13α)-1-Chloro-3,7-dimethoxy-17-methyl-4-(propionyloxy)morphinan-6-yl propionate

The title compound is obtained using the method described in Implementation Example 2 and by using the compound obtained in Implementation Example 3.

Oily matter.

Implementation Example 7: (9α,13α)-1-Chloro-3,4,7-trimethoxy-17-methyl-7,8-didehydromorphinan-6-one

An excess of freshly prepared diasomethane in ether is used to treat 10ml of a solution of methanol containing 400mg of the compound obtained in Implementation Example 1, and the reaction mixture then stirred at ambient temperature for 12 hours. The excess of diazomethane is then broken down using glacial acetic acid, and the solvents evaporated off under reduced pressure. The residue obtained is adjusted to pH = 8-9 using saturated $NaHCO_3$ solution and is then extracted with $CHCl_3$. The organic phase is dried over Na_2SO_4 and vacuum evaporation carried out, then the residue obtained chromatographed on silica gel (eluent $CHCl_3$-MeOH) to yield the title product in the form of an oil.

Implementation Example 8: (9α,13α)-1-Chloro-3,4,7-trimethoxy-17-methyl-7,8-didehydromorphinan-6-ol

The title compound is obtained using the procedure described for Example 4, and by using the compound obtained in Implementation Example 7.

Colourless crystals.

Melting point : 163-165°C.

Implementation Example 9: (9α,13α)-1-Chloro-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one oxime

200mg of NH_2OH . HCl and 300mg of sodium acetate are added to an ethanol solution containing 360mg of the compound obtained in Implementation Example 1. The reaction mixture is then stirred for 4 hours, then filtered and evaporated under reduced pressure. The residue obtained is made alkaline using $NaHCO_3$ solution and extracted with $CHCl_3$. The organic phase is dried over Na_2SO_4 and then evaporated under reduced pressure, the title compound is then obtained in the form of needles by recrystallization from EtOH.

Melting point : 167-169°C.

Implementation Example 10: (9α,13α)-1-Chloro-6-ethoxy-4-hydroxy-3-methoxy-17-methyl-5,6-didehydromorphinan-7-one

SO_2Cl_2 is added at 10°C to a solution of 100ml of $CHCl_3$ containing 10ml of absolute alcohol and 1.3g of the compound obtained in Implementation Example 1, and the reaction mixture stirred for 8 hours. The solvent is then evaporated off under reduced pressure, and the residue neutralised using $NaHCO_3$ and then extracted with $CHCl_3$. The organic phase is dried over Na_2SO_4 and evaporated under reduced pressure, and the title compound obtained in the form of yellowish crystals by recrystallisation from CH_3CN.
Melting point : 190-192°C.

Implementation Example 11: (9α,13α)-1-Chloro-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one hydrazone

A solution of 10ml of 85% hydrazine containing 600 mg of the compound obtained in Implementation Example 1 is stirred at 90°C for 8 hours. After cooling, the reaction mixture is filtered and the solid obtained is washed with water and recrystallized from EtOH to yield the title compound in the form of yellowish crystals.

Melting point : 235-237°C.

Implementation Example 12: (9α,13α)-1-Bromo-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one

A 150ml solution of $CHCl_3$ containing 6.6 g of the compound obtained in Implementation Example 1 is cooled to 0°C, and then dripped whilst stirring into bromine that has been dried with concentrated sulphuric acid, whilst maintaining the temperature of the reaction mixture at 5°C. The reaction is allowed to continue for a few minutes and then neutralisation is carried out using $NaHCO_3$. The organic phase is separated off, dried over Na_2SO_4 and evaporated under reduced pressure, the residue obtained is then recrystallized from EtOH to yield the title compound in the form of brown crystals.

Melting point : 163-165°C.

Implementation Example 13: (9α,13α)-1-Bromo-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4,6-diol

The title compound is obtained using the method described for Implementation Example 4, and using the compound obtained in Implementation Example 12 and replacing $NaBH_4$ with KBH_4.

Solid.

Melting point : 144-146°C.

Implementation Example 14: (9α,13α)-1-Bromo-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one hydrazone

The title compound is obtained using the method described in Implementation Example 11, and using the compound obtained in Implementation Example 12.

Solid.

Melting point : 208-210°C.

Implementation Example 15: (9α,13α)-1-Bromo-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one oxime

The title compound is obtained using the method described in Implementation Example 9, and using the compound obtained in Implementation Example 12.

Solid.

Melting point : 180-182°C.

Implementation Example 16: (9α,13α)-1-Bromo-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one N-oxide

After stirring a mixture of 10ml of H_2O and 820mg of the compound obtained in Implementation Example 12 for 24 hours at room temperature, extract in three stages (30ml X 3) using $CHCl_3$. Using anhydrous Na_2SO_4 dry the amalgamated extract overnight, then remove the solution using evaporation, then add 30ml of cold water to the residue obtained. Collect the resulting solid powder using filtration, then rinse in cold water until the water becomes clear, then recrystallize in ethanol to obtain the solid title compound.

Melting point: 170-172°C.

Implementation Example 17: (9α,13α)-1-Chloro-4-hydroxy-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-6-one N-oxide

After stirring a mixture of 10ml of H_2O and 720mg of the compound obtained in Implementation Example 1 for 24 hours at room temperature, extract in three stages (30ml X 3). Using anhydrous Na_2SO_4 dry the amalgamated extract, then remove the solution using evaporation, then add 30ml of cold water to the residue obtained. Collect the resulting solid white powder using filtration, then recrystallize in ethanol to obtain the solid title compound.

Melting point: 170-172°C.

Implementation Example 18: (9α,13α)-1-Bromo-3,7-dimethoxy-17-methylmorphinan-4,6-diol

The title compound is obtained using the method described in Implementation Example 3 and using the compound obtained in Implementation Example 12.

Melting point: 160-162°C.

Implementation Example 19: (9α,13α)-1-Chloro-6-ethoxy-3-methoxy-17-methyl-5,6-didehydromorphinan-4,7-diol

The title compound is obtained using the method described in Implementation Example 3 and using the compound obtained in Implementation Example 10 whilst exchanging KBH_4 for $NaBH_4$.

Solid.
Melting point: 168-170°C.

Implementation Example 20: (9α,13α)-1-Chloro-6-ethoxy-4-hydroxy-3-methoxy-17-methyl-5,6-didehydromorphinan-7-one oxime

The title compound is obtained using the method described in Implementation Example 9, and using the compound obtained in Implementation Example 10.

Solid.

Melting point : 216-218°C.

Pharmacological study of the compounds of this invention:

EXAMPLE A : Acute toxicity study

Acute toxicity was evaluated after oral administration to groups each comprising 8 mice (26 ± 2 grams). The animals were observed at regular intervals during the course of the first day, and daily for two weeks following treatment. The LD_{50} (dosage that causes the death of 50 % of the animals) was evaluated, demonstrating the low toxicity of the compounds of the invention.

EXAMPLE B : Morris water maze test in mice:

The anti-amnesic effects of the compounds of this invention were evaluated using the Morris mouse water maze test (Morris *et al.*, Nature,1986, 319, 774-776) and using scopolamine as an amnesic agent. Kunming strain mice (18-24g, Shanghai Test Animal Centre) of both sexes were used. Mice were placed in the water maze (80x50x20 cm) and trained to find the platform. After a one day adaptation period, each mouse received 3 daily training sessions over seven days. Mice were trained to a criterion of finding the platform within 20 seconds and with < 2 errors of entering a dead-end. Once a mouse met the criterion, frequency of training was reduced to one daily session until all mice met the criterion. Trained mice were randomly assigned to sub-groups. Compounds under study were dissolved in distilled water and administered orally 40 minutes before behavioural testing. Scopolamine (5 mg/kg, I.P.) was injected 30 minutes before the test. The number of errors and the time for reaching the platform were recorded. Data was expressed as

mean +/- s.e.m. Statistical analysis was performed using ANOVA followed by Duncan's multiple-range test.

Results demonstrate that compounds of the present invention were capable of counteracting scopolamine-induced memory impairments in a dose-dependent manner (from 20 to 100 mg/kg) in the Morris mouse water maze test, indicating that such compounds possess anti-amnesic properties.

EXAMPLE C : Social recognition in the Wistar rat

Initially described in 1982 by THOR and HOLLOWAY (J. Comp. Physiol., 1982, 96, 1000-1006), the social recognition test has subsequently been proposed by various authors (DANTZER et al., Psychopharmacology, 1987, 91, 363-368 ; PERIO et al., Psychopharmacology, 1989, 97, 262-268) for studying the memory/cognitive effects of new compounds. This test is based on the natural expression of the olfactory memory of the rat and its natural tendency to forget, and allows evaluation of memory, based on recognition of immature animals of the same species by adult rats. An immature rat (21 days) is selected at random, and placed for 5 minutes in a cage housing an adult rat. With the aid of a video installation, the researcher observes the social behaviour of the adult rat and measures its overall duration. The immature rat is then removed from the adult rat's cage and is placed in its own cage to await the second test introduction. The adult rat is given the test compound and, after 2 hours, is again placed together (5 minutes) with the immature rat. The social behaviour is then observed again and its duration measured. The assessment criterion is the difference (T_2-T_1), expressed in seconds, between the "recognition" times of the 2 encounters.

The results obtained show a difference between (T_2-T_1) ranging from (–10) s to (–33) s for doses ranging from 3 to 30 mg/kg, demonstrating the great capacity of compounds of this invention to strengthen the memory.

EXAMPLE D : Object recognition in the Wistar rat

The object recognition test for Wistar rats was initially developed by ENNACEUR and DELACOUR (Behv. Brain Res., 1988, 31, 47-59). The test takes into account the

spontaneous exploratory ability of animals, as this presents characteristics of episodic memory exhibited by humans. This memory test is capable of detecting ageing (SCALI et al., Eur. J. Pharmacol., 1997, 325, 173-180) and cholinergic dysfunctions (BARTOLINI et al., Pharm. Biochem. Behav. 1996, 53(2), 277-283) and is based on the differences in exploratory activity when presented with 2 objects of fairly similar shape (one being familiar, the other new). Prior to the test, the animals are familiarized with the environment (an enclosure without an object). In the course of a first session, the rats are placed (3 minutes) in an enclosure within which there are 2 identical objects. The duration of exploration is measured for each object. In the course of the second session (3 minutes), commenced 24 hours later, 1 of the 2 objects is replaced by a new object. The duration of exploration is measured for each object. The assessment criterion is the difference (Δ), expressed in seconds, between the exploration times for the new object and for the familiar object in the course of the second session. The control animals, previously treated with an I.P. administered carrier 30 minutes before each session, explored the familiar objects and the new objects in a similar manner, demonstrating that objects introduced earlier had already been forgotten. Animals treated with a compound that enhances memory/cognition exhibited a preference to explore the new objects, demonstrating that objects introduced earlier had been remembered.

The results obtained showed a difference, (Δ), ranging from 5 to 11 s, for doses ranging from 0.3 to 10 mg/kg, demonstrating that compounds of this invention greatly enhance memory.

EXAMPLE E : $NANO_2$ induced hypoxia in mice

The neuro-protective function of compounds of this invention were evaluated in mice. Kunming strain mice of both sexes were provided by the Shanghai Test Animal Centre of the China Academy of Sciences (clean grade, certificate number 005). Mice of 22-28g weight were kept in an environment with regular 12 hour periods of light and dark and free access to food and drink. The compounds to be tested were dissolved in a 5% solution of polysorbate 80 and a 50mg/kg dosage given orally 60 minutes prior to I.P. administration of 225mg/kg of $NaNO_2$. The death rate was observed, and the duration for which mice remained alive recorded. The results demonstrate that compounds of this

invention when given orally in 50mg/kg doses have the ability of prolonging the lives of mice to which $NaNO_2$ has been administered intraperitoneally. This demonstrates that compounds of this invention exhibit pronounced anti-hypoxic and neuro-protective properties.

EXAMPLE F : Pharmaceutical composition

Formula for the preparation of 1000 tablets each containing 10 mg of active ingredient: (9α,13α)-1-chloro-3,7-dimethoxy-17-methyl-7,8-didehydromorphinan-4,6-diol (Implementation Example 4) ..... 10 g
hydroxypropylcellulose..... 2 g
wheat starch ..... 10 g
lactose ..... 100 g
magnesium stearate..... 3 g
talc..... 3 g

Appended Diagrams:

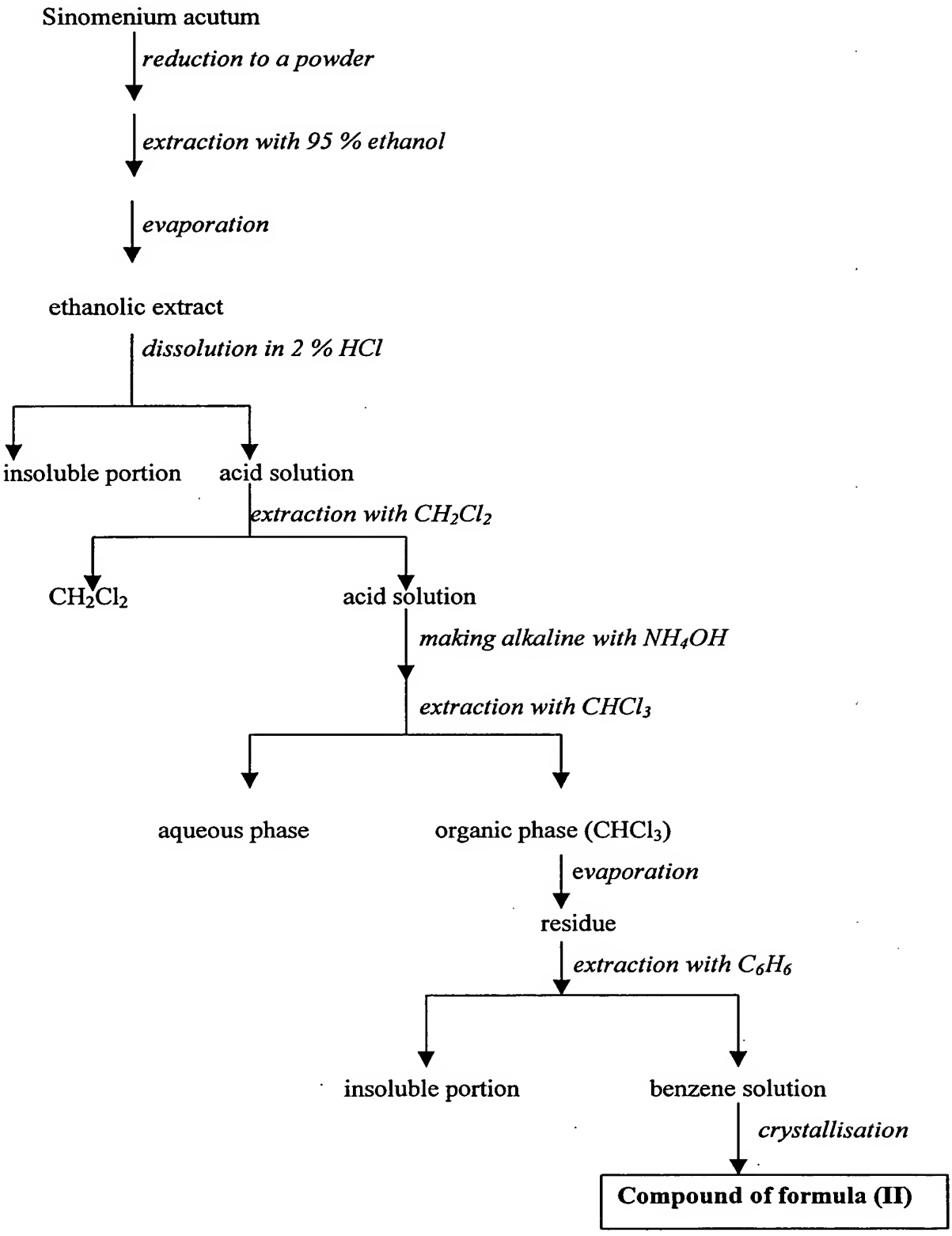


Diagram 1 : Extraction of the compound of formula (II)

SINONENINE

证　　明

本证明之附件是向本局提交的下列专利申请副本

申　　日：2002.11.28

申　请　号：02153819.0

申 请 类 别：发明

发明创　　：汉防己碱和汉防己碱化合物，合成和应用

申　请　人：中国科学院上海药物研究所　瑟维尔实验室

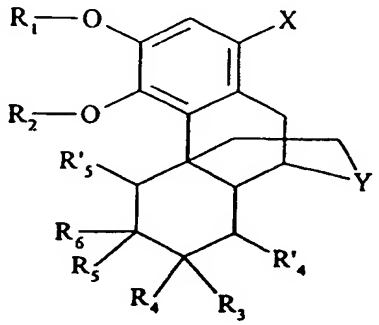
发明人或设计人：秦国伟、唐希灿、王蕊、周天锡、P ·莱塔热、D - H ·凯尼亚尔、P ·勒纳尔

中华人民共和国
国家知识产权局局长　王景川

2005 年 1 月 14 日

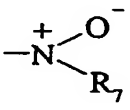
权 利 要 求 书

1. 式(I)化合物、其对映体和非对映体及其与可药用酸或碱的加成盐，



(I),

其中

- R_1是烷基，
- R_2是氢原子或烷基羰基，
- Y是基团NR_7或  其中R_7是烷基，
- R_3是羟基或烷氧基，
- R_4和R'_4各是氢原子或一起形成另一键，或R_3和R_4一起形成氧代基团或=N-OR_8，其中R_8是氢原子或烷基，
- R_6是羟基，其中烷基部分可以被羟基、烷氧基、羧基或烷氧羰基取代的烷基羰氧基，或烷氧基，
- R_5和R'_5各是氢原子或一起形成另一键，或R_5和R_6一起形成氧代基团、=N-OR_9或=N-$NR_{10}R_{11}$，其中R_9、R_{10}和R_{11}可以相同或不同，各是氢原子或烷基，
- 以及X是卤原子，

条件是式(I)化合物不能是 1-溴-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮，

应当理解的是：

- “烷基”是指含有 1-6 个碳原子的直链或支链烷基，

－“烷氧基”是指含有 1-6 个碳原子的直链或支链烷氧基。

2. 根据权利要求 1 的式(I)化合物、其对映体和非对映体及其与可药用酸或碱的加成盐，其中 R_1 是甲基。

3. 根据权利要求 1 的式(I)化合物、其对映体和非对映体及其与可药用酸或碱的加成盐，其中 R_2 是氢原子。

4. 根据权利要求 1 的式(I)化合物、其对映体和非对映体及其与可药用酸或碱的加成盐，其中 R_2 是烷基羰基。

5. 根据权利要求 1 的式(I)化合物、其对映体和非对映体及其与可药用酸或碱的加成盐，其中 R_2 是乙基羰基。

6. 根据权利要求 1 的式(I)化合物、其对映体和非对映体及其与可药用酸或碱的加成盐，其中 Y 是基团 NR_7。

7. 根据权利要求 1 的式(I)化合物、其对映体和非对映体及其与可药用酸或碱的加成盐，其中 X 是氯原子。

8. 根据权利要求 1 的式(I)化合物、其对映体和非对映体及其与可药用酸或碱的加成盐，其中 X 是溴原子。

9. 根据权利要求 1 的式(I)化合物、其对映体和非对映体及其与可药用酸或碱的加成盐，其中 R_3 是烷氧基且 R_4 和 R'_4 一起形成另一键。

10. 根据权利要求 1 的式(I)化合物、其对映体和非对映体及其与可药用酸或碱的加成盐，其中 R_5 是氢原子。

11. 根据权利要求 1 的式(I)化合物、其对映体和非对映体及其与可药用酸或碱的加成盐，其中 R_6 是 OH 基团。

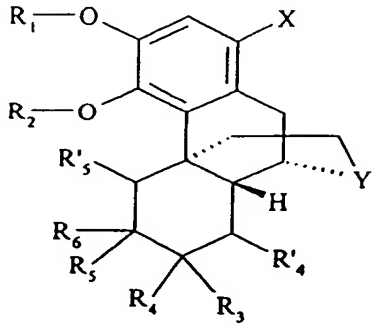
12. 根据权利要求 1 的式(I)化合物、其对映体和非对映体及其与可药用酸或碱的加成盐，其中 R_6 是烷基羰氧基。

13. 根据权利要求 1 的式(I)化合物，其是(9α,13α)-1-氯-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-4,6-二醇。

14. 根据权利要求 1 的式(I)化合物，其是丙酸(9α,13α)-1-氯-3,7-二甲氧基-17-甲基-4-(丙酰氧基)-7,8-二脱氢吗啡喃-6-基酯。

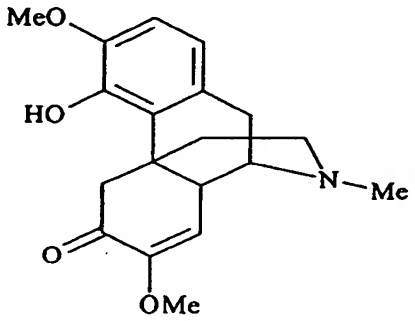
15. 根据权利要求 1 的式(I)化合物和其与可药用酸或碱的加成盐，其

中所述式(I)化合物具有如下式(I')所示构型：



(I')

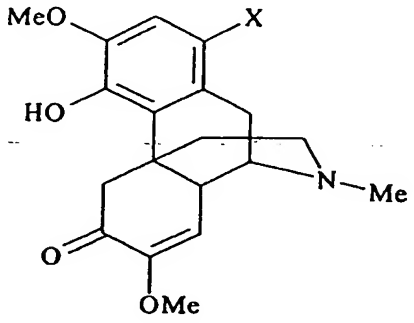
16. 制备根据权利要求1的式(I)化合物的方法，其特征在于使用式(II)化合物作为原料：



(II),

其中所述式(II)化合物是从青藤的茎中提取得到的；

将所述式(II)化合物与卤化剂如 SO_2Cl_2 或 Br_2 反应，获得式(I/a)化合物—式(I)化合物的特例：



(I/a),

其中 X 如式(I)中所定义，对此式(I/a)化合物进行常规化学反应以获得全部式(I)化合物，其可以根据常规分离技术纯化，并在期望时转化为与可药用酸或碱的加成盐，而且如果适当的话可以根据常规分离技术分离成其异构体。

17. 药物组合物，包含至少一种根据权利要求 1-15 之任一项的式(I)化合物或其与可药用酸或碱的加成盐以及一种或多种可药用赋形剂。

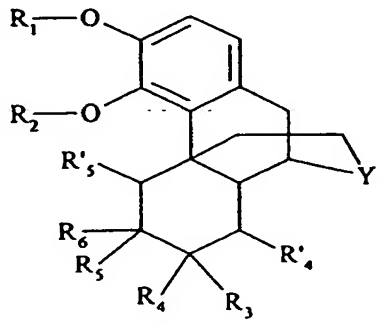
18. 根据权利要求 17 的药物组合物在制备用于治疗与脑老化及与神经变性疾病如阿尔茨海默氏病、帕金森氏病、皮克病、科尔萨科夫精神病以及额叶和皮质下痴呆有关的记忆缺陷的药物中的用途。

19. 汉防己碱和/或汉防己碱化合物在获取旨在用于治疗与脑老化及与神经变性疾病如阿尔茨海默氏病、帕金森氏病、皮克病、科尔萨科夫精神病以及额叶和皮质下痴呆有关的记忆缺陷的药物组合物中的用途。

20. 根据权利要求 19 的汉防己碱在获取旨在用于治疗与脑老化及与神经变性疾病如阿尔茨海默氏病、帕金森氏病、皮克病、科尔萨科夫精神病以及额叶和皮质下痴呆有关的记忆缺陷的药物组合物中的用途。

21. 根据权利要求 19 的汉防己碱化合物在获取旨在用于治疗与脑老化及与神经变性疾病如阿尔茨海默氏病、帕金森氏病、皮克病、科尔萨科夫精神病以及额叶和皮质下痴呆有关的记忆缺陷的药物组合物中的用途。

22. 根据权利要求 19 的式(Ia)的汉防己碱化合物 在获取旨在用于治疗与脑老化及与神经变性疾病如阿尔茨海默氏病、帕金森氏病、皮克病、科尔萨科夫精神病以及额叶和皮质下痴呆有关的记忆缺陷的药物组合物中的用途:



(Ia),

其中 R_1、R_2、R_3、R_4、R'_4、R_5、R'_5、R_6和 Y 如权利要求 1 中的定义。

23. 根据权利要求 19 的汉防己碱化合物在获取旨在用于治疗与脑老化及与神经变性疾病如阿尔茨海默氏病、帕金森氏病、皮克病、科尔萨科夫精神病以及额叶和皮质下痴呆有关的记忆缺陷的药物组合物中的用途，

其中所述汉防己碱化合物是：(9α,13α)-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮腙；(7α,9α,13α)-4-羟基-3,7-二甲氧基-17-甲基吗啡喃-6-酮；(7β,9α,13α)-4-羟基-3,7-二甲氧基-17-甲基吗啡喃-6-酮；丙酸(9α,13α)-3,7-二甲氧基-17-甲基-6-氧代-7,8-二脱氢吗啡喃-4-基酯；(9α,13α)-3,4,7-三甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮；(9α,13α)-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮肟；(9α,13α)-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-4,6-二醇；(9α,13α)-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮 N-氧化物；(9α,13α)-6-氨基-3,7-二甲氧基-17-甲基吗啡喃-4-醇；4-{[(9α,13α)-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-基]-氧基}-4-氧代丁酸；丙酸(9α,13α)-3,7-二甲氧基-17-甲基-4-(丙酰氧基)-7,8-二脱氢吗啡喃-6-基酯。

24. 药物组合物，包含汉防己碱或汉防己碱化合物及一种或多种可药用赋形剂，用于治疗与脑老化及与神经变性疾病如阿尔茨海默氏病、帕金森氏病、皮克病、科尔萨科夫精神病以及额叶和皮质下痴呆有关的记忆缺陷。

<PN 020919>

说　　明　　书

汉防己碱和汉防己碱化合物，合成和应用

青藤(*Sinomenum acutum*)是一种木质藤本植物，其广泛分布在中国的中部、东南和西南部，并被包括在中国药典(中华人民共和国药典委员会，2000)中。它含有大量不同化学结构的生物碱，如汉防己碱、清风藤碱、乙基汉防己碱、双汉防己碱、四氢表小檗碱、青藤碱和木兰花碱(Huang Tai-Kang，《常用中药的组成和药理学手册》(*Handbook of the Composition and Pharmacology of Common Chinese Drugs*)，中国医学科技出版社，1994，北京，1156-1160)。

汉防己碱是一种吗啡样生物碱并是所述植物的主要成分，对它的研究已有很多；尤其是，其可能表现出抗炎、免疫抑制、抗心率不齐和止痛性质(Qiang Liu 等，Chinese Traditional and Herbal Drugs(中草药)，1997，28(4)，247)。

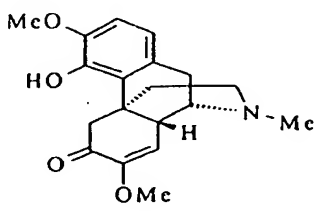
目前我们发现汉防己碱在动物实验模型中有促进记忆认知的性质。

由预期寿命延长造成的人口老化引起与正常脑老化或神经变性疾病(如阿尔茨海默氏病)过程中的病理性脑老化有关的认知障碍大大增加。

现今用于治疗与衰老有关的认知障碍的大多数物质通过促进中枢胆碱能系统－在乙酰胆碱酯酶抑制剂(他克林、多萘哌齐(donepezil))和胆碱能激动剂(奈非西坦)的情况下直接促进，或在精神功能改善剂(nootropic agent)(吡拉西坦、普拉西坦)和脑血管扩张药(长春西汀)的情况下间接促进。

因此，尤其有价值的是合成能够对抗与衰老相关的认知障碍和/或改善认知活动的新化合物。

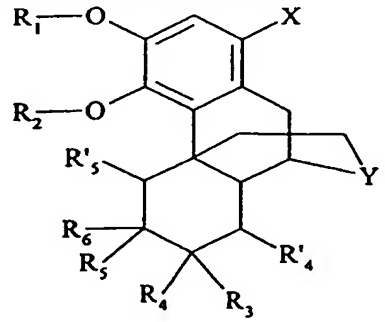
本发明一方面涉及汉防己碱



和/或汉防己碱化合物在记忆认知障碍中的用途，另一方面涉及在相同领域具有特别有价值的药理学性质的新化合物的合成。

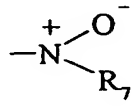
图 1 为在本发明中用作原料的式(II)化合物的提取流程图。

更具体地，本发明涉及式(I)化合物：



(I),

其中

- R_1 是烷基，
- R_2 是氢原子或烷基羰基，
- Y 是基团 NR_7 或  其中 R_7 是烷基，
- R_3 是羟基或烷氧基，
- R_4 和 R'_4 各是氢原子或一起形成另一键，或 R_3 和 R_4 一起形成氧代基团或=N-OR_8，其中 R_8 是氢原子或烷基，
- R_6 是羟基，其中烷基部分可以被羟基、烷氧基、羧基或烷氧羰基取代的烷基羰氧基，或烷氧基，
- R_5 和 R'_5 各是氢原子或一起形成另一键，或 R_5 和 R_6 一起形成氧代基团、=N-OR_9 或=N-$NR_{10}R_{11}$，其中 R_9、R_{10} 和 R_{11} 可以相同或不同，各是氢原子或烷基，
- 以及 X 是卤原子，

条件是式(I)化合物不能是 1-溴-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮，

应当理解的是：

- “烷基”是指含有 1-6 个碳原子的直链或支链烷基，

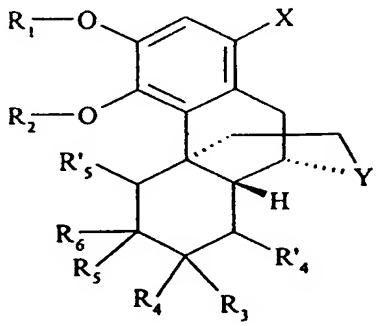
– “烷氧基”是指含有 1-6 个碳原子的直链或支链烷氧基，

并涉及式(I)化合物的对映体和非对映体，及其与可药用酸或碱的加成盐。

在所述可药用酸中可以提及的有，但不限于，盐酸、氢溴酸、硫酸、磷酸、乙酸、三氟乙酸、乳酸、丙酮酸、丙二酸、琥珀酸、戊二酸、富马酸、酒石酸、马来酸、柠檬酸、抗坏血酸、甲磺酸、樟脑酸、草酸等。

在所述可药用碱中可以提及的有，但不限于，氢氧化钠、氢氧化钾、三乙胺、叔丁基胺等。

根据本发明的式(I)化合物的优选构型如式(I')所示：



(I')

优选的 R_1 基团是甲基。

有利的是，R_2 是氢原子或基团 EtCO。

Y 优选是基团 NR_7，更优选是基团 N-Me。

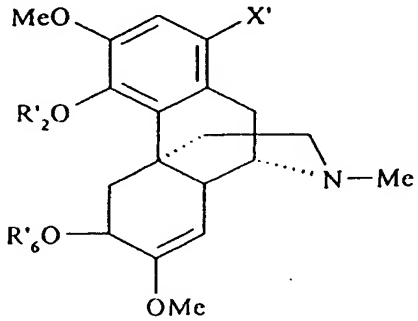
X 非常优选是氯或溴原子。

有利地，本发明涉及式(I)的化合物，其中 R_3 是烷氧基且 R_4 和 R'_4 一起形成另一键。

R_5 优选是氢原子。

R_6 有利地是 OH 或烷基羰氧基，更尤其是乙基羰氧基。

非常优选的是本发明涉及式(I'')化合物：



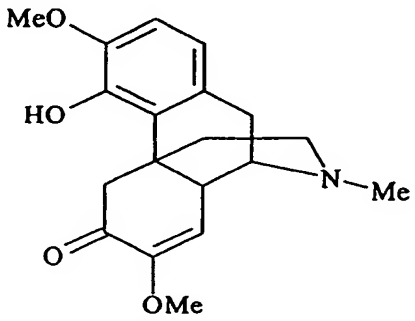
(I'')

其中 R'_2 和 R'_6 可以相同或不同，是氢原子或烷基羰基，且 X'是氯或溴原子。

甚至更优选地，本发明涉及如下式(I)化合物，其是(9α,13α)-1-氯-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-4,6-二醇和丙酸(9α,13α)-1-氯-3,7-二甲氧基-17-甲基-4-(丙酰氧基)-7,8-二脱氢吗啡喃-6-基酯。

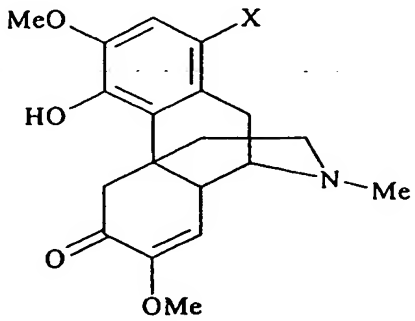
本发明优选化合物的对映体和非对映体及其与可药用酸或碱的加成盐构成了本发明的一个完整部分。

本发明还涉及制备式(I)化合物的方法，该方法的特征在于使用式(II)化合物作为原料：



(II),

其中所述式(II)化合物是根据附图 1 从青藤的茎中提取得到的；
将所述式(II)化合物与卤化剂如 SO_2Cl_2 或 Br_2 反应，获得式(I/a)化合物－式(I)化合物的特例：



(I/a),

其中 X 如式(I)中所定义，对此式(I/a)化合物进行常规化学反应以获得全部式(I)化合物，其可以根据常规分离技术纯化，并在期望时转化为与可药用酸或碱的加成盐，而且如果适当的话可以根据常规分离技术分离成其异构

体。

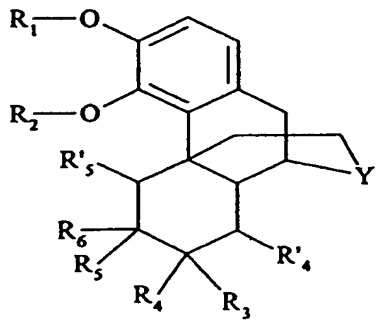
除了本发明化合物是新的这一事实外，它们还具有促进认知活动的性质，这使得它们可以用于治疗与脑老化及与神经变性疾病有关的认知缺陷，其中所述神经变性疾病有如阿尔茨海默氏病、帕金森氏病、皮克病、科尔萨科夫精神病以及额叶和皮质下痴呆。

本发明还涉及包含至少一种式(I)化合物作为活性成分并包含一种或多种适当的惰性非毒性赋形剂的药物组合物。

本申请人还发现汉防己碱和/或汉防己碱化合物具有促进记忆认知的性质。

因此，本发明还涉及汉防己碱和/或汉防己碱化合物在获取用于治疗与脑老化及与神经变性疾病有关的认知缺陷的药物组合物中的用途，其中所述神经变性疾病有例如阿尔茨海默氏病、帕金森氏病、皮克病、科尔萨科夫精神病以及额叶和皮质下痴呆。

更特别地，本发明涉及汉防己碱和/或汉防己碱化合物如式(Ia)的化合物在获取用于治疗与脑老化及与神经变性疾病有关的认知缺陷的药物组合物中的用途，其中所述神经变性疾病有例如阿尔茨海默氏病、帕金森氏病、皮克病、科尔萨科夫精神病以及额叶和皮质下痴呆，所述式(Ia)化合物是：



(Ia),

其中 R_1、R_2、R_3、R_4、R'_4、R_5、R'_5、R_6和 Y 如式(I)中所定义，且所述化合物更具体地是(9α,13α)-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮腙；(7α,9α,13α)-4-羟基-3,7-二甲氧基-17-甲基吗啡喃-6-酮；(7β,9α,13α)-4-羟基-3,7-二甲氧基-17-甲基吗啡喃-6-酮；丙酸(9α,13α)-3,7-二甲氧基-17-甲基-6-氧代-7,8-二脱氢吗啡喃-4-基酯；(9α,13α)-3,4,7-三甲氧基

-17-甲基-7,8-二脱氢吗啡喃-6-酮；(9α,13α)-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮肟；(9α,13α)-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-4,6-二醇；(9α,13α)-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮 N-氧化物；(9α,13α)-6-氨基-3,7-二甲氧基-17-甲基吗啡喃-4-醇；4-{[(9α,13α)-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-基]-氧基}-4-氧代丁酸；丙酸(9α,13α)-3,7-二甲氧基-17-甲基-4-(丙酰氧基)-7,8-二脱氢吗啡喃-6-基酯。

本发明的一个有利方面涉及汉防己碱在获取用于治疗与脑老化及与神经变性疾病有关的认知缺陷的药物组合物中的用途。

本发明另一尤其有意义的方面涉及式(Ia)化合物在获取用于治疗与脑老化及与神经变性疾病有关的认知缺陷的药物组合物中的用途，所述式(Ia)化合物更特别地是(9α,13α)-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮腙；(7α,9α,13α)-4-羟基-3,7-二甲氧基-17-甲基吗啡喃-6-酮；(7β,9α,13α)-4-羟基-3,7-二甲氧基-17-甲基吗啡喃-6-酮；丙酸(9α,13α)-3,7-二甲氧基-17-甲基-6-氧代-7,8-二脱氢吗啡喃-4-基酯；(9α,13α)-3,4,7-三甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮；(9α,13α)-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮肟；(9α,13α)-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-4,6-二醇；(9α,13α)-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮 N-氧化物；(9α,13α)-6-氨基-3,7-二甲氧基-17-甲基吗啡喃-4-醇；4-{[(9α,13α)-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-基]氧基}-4-氧代丁酸；丙酸(9α,13α)-3,7-二甲氧基-17-甲基-4-(丙酰氧基)-7,8-二脱氢吗啡喃-6-基酯。

本发明还涉及包含汉防己碱或其化合物以及一种或多种可药用赋形剂的药物组合物，该组合物用于治疗与脑老化及与神经变性疾病如阿尔茨海默氏病、帕金森氏病、皮克病、科尔萨科夫精神病以及额叶和皮质下痴呆有关的认知缺陷。

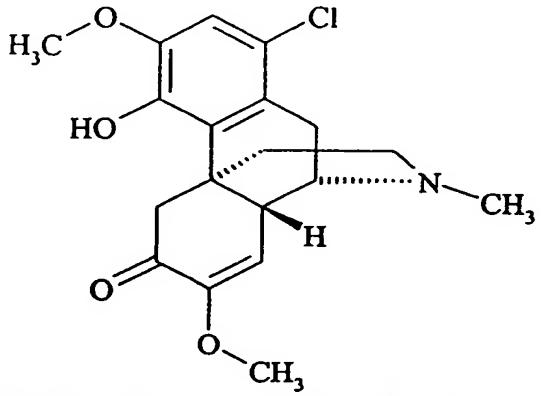
在根据本发明的药物组合物中，更为特别地可以提及的是适于口服、胃肠外(静脉内或皮下)或鼻腔给药的那些，片剂或糖衣丸，舌下片，明胶

胶囊，锭剂，栓剂，霜剂，软膏，皮肤凝胶，可注射制剂，可饮用悬浮液等。

有用的剂量可以根据疾病的性质和严重性、给药途径以及患者的年龄和体重的不同而改变。剂量变化范围为每天 0.01mg-1g，一次或多次给药。

如下实施例举例说明本发明，但不以任何方式构成限制。

实施例 1: (9α,13α)-1-氯-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮



向 100mg 式(II)化合物的 5ml $CHCl_3$ 溶液中加入 3 滴 SO_2Cl_2。室温下搅拌反应混合物 4 小时，并用 $NaHCO_3$ 溶液将 pH 调节至 7-8; 然后用 $CHCl_3$ 进行萃取。在减压下蒸发有机相，使用 $CHCl_3$-MeOH(9:1)洗脱液在硅胶上对所获残余物进行层析，产生黄色固体标题化合物。

熔点: 126-128℃。

实施例 2: 丙酸(9α,13α)-1-氯-3,7-二甲氧基-17-甲基-6-氧代-7,8-二脱氢吗啡喃-4-基酯

向 500mg 实施例 1 所获化合物和 100mg DMAP 的 15ml 吡啶溶液中缓慢加入 2ml 丙酸酐，室温搅拌此反应混合物 3 小时。然后蒸发反应混合物并将所获残余物溶解在少量水中。用 $NaHCO_3$ 溶液调节所获溶液的 pH 至 8-9，然后用 $CHCl_3$ 进行萃取。有机相用水洗涤 3 次，经硫酸钠干燥后进行蒸发。使用 $CHCl_3$-MeOH(20:1)洗脱液在硅胶上对所获残余物进行层析，产生无色油状标题化合物。

实施例 3: (6β,7β,9α,13α)-1-氯-3,7-二甲氧基-17-甲基吗啡喃-4,6-二醇

将 720mg 实施例 1 化合物和 100mgPtO_2 在 50ml 无水乙醇中的混合物

于室温及 H_2 气氛下搅拌 12 小时。通过过滤除去 PtO_2，并真空蒸发乙醇，得到糖浆状残余物。用热的无水乙醇(10ml)洗涤此残余物，通过过滤收集得到的粉末状固体，然后在 $CHCl_3/C_2H_5OH$ 中结晶，产生白色晶体状标题化合物。

熔点：210-212℃。

实施例 4：(9α,13α)-1-氯-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-4,6-二醇

向 500mg 实施例 1 所获化合物的 15ml 甲醇溶液中加入 500mg$NaBH_4$，并搅拌反应混合物 1.5 小时。然后蒸发掉甲醇，并用 $CHCl_3$ 萃取所获残余物。有机相通过 Na_2SO_4 干燥后在减压下蒸发。通过从 Et_2O 中重结晶得到白色晶体形式的标题化合物。

熔点：118-120℃。

实施例 5：丙酸(9α,13α)-1-氯-3,7-二甲氧基-17-甲基-4-(丙酰氧基)-7,8-二脱氢吗啡喃-6-基酯

以实施例 4 获得的化合物开始，使用实施例 2 所述方法得到标题化合物。

油状物。

实施例 6：丙酸(6β,7β,9α,13α)-1-氯-3,7-二甲氧基-17-甲基-4-(丙酰氧基)吗啡喃-6-基酯

以实施例 3 获得的化合物开始，使用实施例 2 所述方法得到标题化合物。

油状物。

实施例 7：(9α,13α)-1-氯-3,4,7-三甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮

用过量的新制备的重氮甲烷在乙醚中的制剂处理 400mg 实施例 1 化合物的 10ml 甲醇溶液，并室温搅拌反应混合物 12 小时。然后使用冰醋酸分解多余的重氮甲烷，并在减压下蒸发除去溶剂。用饱和 $NaHCO_3$ 溶液将所获残余物的 pH 调节至 8-9，然后用 $CHCl_3$ 萃取。使用 Na_2SO_4 干燥有机相并真空干燥，然后在硅胶上层析所获残余物(洗脱液 $CHCl_3$-MeOH)，得到油状标题产物。

实施例 8: (9α,13α)-1-氯-3,4,7-三甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-醇

以实施例 7 所获化合物开始，使用实施例 4 所述方法得到标题化合物。无色晶体。

熔点: 163-165℃。

实施例 9: (9α,13α)-1-氯-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮肟

向 360mg 实施例 1 所获化合物的乙醇溶液中加入 200mg$NH_2OH \cdot HCl$ 和 300mg 乙酸钠。搅拌反应混合物 4 小时；然后过滤并在减压下蒸发。所获残余物使用 $NaHCO_3$ 溶液调节成碱性，并用 $CHCl_3$ 萃取。有机相经 Na_2SO_4 干燥后在减压下蒸发，通过从 EtOH 中重结晶得到针状标题化合物。

熔点: 167-169℃。

实施例 10: (9α,13α)-1-氯-6-乙氧基-4-羟基-3-甲氧基-17-甲基-5,6-二脱氢吗啡喃-7-酮

10℃下向 1.3g 实施例 1 所获化合物在 100ml$CHCl_3$和 10ml 无水乙醇中的溶液中加入 SO_2Cl_2，并搅拌反应混合物 8 小时。然后在减压下蒸发掉溶剂，并使用 $NaHCO_3$ 中和残余物，然后用 $CHCl_3$ 萃取。有机相经 Na_2SO_4 干燥后在减压下蒸发，通过从 CH_3CN 中重结晶得到淡黄色晶体标题化合物。

熔点: 190-192℃。

实施例 11: (9α,13α)-1-氯-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮腙

90℃下搅拌 600mg 实施例 1 所获化合物在 10ml85%肼中的溶液 8 小时。冷却后，过滤反应混合物，用水洗涤所获固体并从 EtOH 中重结晶，得到淡黄色晶体标题化合物。

熔点: 235-237℃。

实施例 12: (9α,13α)-1-溴-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮

将 6.6g 实施例 1 所获化合物在 150ml$CHCl_3$ 中的溶液冷却至 0℃，搅拌下滴加经浓硫酸干燥过的溴，同时使反应混合物维持在 5℃。继续该反应几分钟，然后使用 $NaHCO_3$ 进行中和。分离出有机相，经 Na_2SO_4 干燥后在减压下蒸发，所获残余物从 EtOH 中重结晶，得到棕色晶体标题化合物。

熔点：163-165℃。

实施例 13：(9α,13α)-1-溴-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-4,6-二醇

以实施例 12 所获化合物开始并将 $NaBH_4$ 替换成 KBH_4，使用实施例 4 所述方法得到标题化合物。

固体。

熔点：144-146℃。

实施例 14：(9α,13α)-1-溴-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮腙

以实施例 12 所获化合物开始，使用实施例 11 所述方法得到标题化合物。

固体。

熔点：208-210℃。

实施例 15：(9α,13α)-1-溴-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮肟

以实施例 12 所获化合物开始，使用实施例 9 所述方法得到标题化合物。

固体。

熔点：180-182℃。

实施例 16：(9α,13α)-1-溴-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮 N-氧化物

室温搅拌实施例 12 化合物(820mg)在 H_2O_2(10ml)中的混合物 24 小时，然后用 $CHCl_3$ 萃取 3 次(30ml × 3)。用无水 Na_2SO_4 过夜干燥合并的萃取物，并通过蒸发除去溶剂，向所获残余物中加入 30ml 冷水。过滤收集粉末固体，用冷水洗涤直到水变为无色为止，然后在乙醇中结晶得到固体标题化

合物。

熔点：170-172℃。

实施例 17：(9α,13α)-1-氯-4-羟基-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-6-酮 N-氧化物

室温搅拌实施例 1 化合物(720mg)在 H_2O_2(10ml)中的混合物 24 小时，然后萃取 3 次(25ml × 3)。用无水 Na_2SO_4 干燥合并的萃取物，并通过蒸发除去溶剂。将 30ml 冷水加入所获残余物中。过滤收集产生的白色粉末固体，并在乙醇中结晶得到固体标题化合物。

熔点：170-172℃。

实施例 18：(9α,13α)-1-溴-3,7-二甲氧基-17-甲基吗啡喃-4,6-二醇

以实施例 12 所获化合物开始，使用实施例 3 所述方法获得标题化合物。

熔点：160-162℃。

实施例 19：(9α,13α)-1-氯-6-乙氧基-3-甲氧基-17-甲基-5,6-二脱氢吗啡喃-4,7-二醇

以实施例 10 所获化合物开始并用 KBH_4 替换 $NaBH_4$，使用实施例 4 所述方法得到标题化合物。

固体。

熔点：168-170℃。

实施例 20：(9α,13α)-1-氯-6-乙氧基-4-羟基-3-甲氧基-17-甲基-5,6-二脱氢吗啡喃-7-酮肟

以实施例 10 所获化合物开始，使用实施例 9 所述方法得到标题化合物。

固体。

熔点：216-218℃。

本发明化合物的药理学研究

实施例 A：急性毒性研究

在给各包含 8 只小鼠(26 ± 2 克)的实验组口服给药后，评价急性毒性。在第一天以及处理后的两周内每天定期观察动物。评价 LD_{50}(引起 50％动

物死亡的剂量)，证实本发明化合物具有低毒性。

实施例 B: 小鼠 Morris 水迷宫试验

使用小鼠 Morris 水迷宫试验(Morris 等，Nature(自然)，1986，319，774-776)并以东莨菪碱作为遗忘剂，评价本发明化合物的抗遗忘作用。使用不同性别的昆明(Kumming)系小鼠(18-24g，上海实验动物中心)。将小鼠放入水迷宫(80 × 50 × 20cm)，并训练其寻找平台。适应一天后，每只小鼠接受每日 3 次的训练，共 7 天。小鼠被训练达到如下标准：20 秒内找到平台，且进入死端的错误小于 2 次。一旦小鼠达到此标准，即减少训练次数至每天一次直到所有的小鼠均符合标准。将训练过的小鼠随机分组。把待研究的化合物溶解在蒸馏水中，并通过口服途径在行为试验前 40 分钟给药。试验前 30 分钟注射东莨菪碱(5mg/kg，腹膜内)。记录出错的次数和达到平台的时间。数据表示为平均值+/-s.e.m。使用 ANOVA 进行统计学分析，随后进行 Duncan 氏多范围检验。

结果证实在小鼠 Morris 水迷宫试验中本发明化合物能够以剂量依赖性方式(20-100mg/kg)抵制东莨菪碱诱导的记忆损伤，说明该化合物具有抗遗忘性质。

实施例 C: Wistar 大鼠的社会认知

社会认知实验最初在 1982 年由 THOR 和 HOLLOWAY 描述过(J. Comp. Physiol.，1982，96，1000-1006)，随后被许多作者(DANTZER 等，Psychopharmacology(精神药理学)，1987，91，363-368; PERIO 等，Psychopharmacology，1989，97，262-268)提议用于研究新化合物的记忆认知作用。该实验基于大鼠嗅觉记忆的自然表达和其遗忘的天然倾向，这就使得可以通过成年大鼠对幼年同类动物的识别来评价记忆力。将随机取得的幼年大鼠(21 天)放入装有成年大鼠的笼子中 5 分钟。在视频装置的帮助下，实验员观察成年大鼠的社会认知行为并测量整个持续时间。然后将幼年大鼠从成年大鼠的笼子中取出并在第二次引入实验前将其置于自己的笼子中。给予成年大鼠测试化合物，并在 2 小时后再次使其和幼年大鼠相处(5 分钟)。然后再次观察社会认知行为，并测量持续时间。评价的标准是

2 次相处的“识别”时间之间的差异(T_2-T_1)，以秒表示。

所获结果表明对于 3-30mg/kg 的剂量，差异(T_2-T_1)的范围为(-10)s-(-33)s，这说明本发明化合物极大地增强了记忆力。

实施例 D: Wistar 大鼠的物体识别

Wistar 大鼠的物体识别实验最初由 ENNACEUR 和 DELACOUR 建立(Behv. Brain Res.(行为与脑研究)，1988，31，47-59)。该实验基于动物的自发探索活动，在人类中具有偶然记忆的特征。该记忆实验对衰老(SCALI 等，Eur. J. Pharmacol.(欧洲药理学杂志)，1997，325，173-180)和胆碱能功能障碍(BARTOLINI 等，Pharm. Biochem. Behav.(药学、生物化学和行为)，1996，53(2)，277-283)敏感，且基于对形状较类似的 2 个物体(一个是熟悉的，另一个是新的)进行的探索的差异。在实验前，使动物熟悉环境(没有物体的罩子)。在第一步阶段，将大鼠放入内有两个相同物体的罩内(3 分钟)。测量对每个物体的探索持续时间。在 24 小时后的第二阶段(3 分钟)，将 2 个物体中的一个替换成新的物体。测量对每个物体的探索持续时间。评价标准是在第二阶段中对新物体的探索时间与对熟悉物体的探索时间之间的差异(Δ)，以秒表示。早先在每个阶段前 30 分钟通过腹膜内途径用载体处理过的对照动物以相同的方式探索熟悉物体和新物体，这说明较早引入的物体已被忘记。用促进记忆认知的化合物处理的动物优先探索新物体，这说明较早引入的物体已被记住。

所获结果表明对于 0.3-10mg/kg 的剂量，差异(Δ)范围为 5-11s，这说明本发明化合物极大地增强了记忆力。

实施例 E: $NANO_2$ 诱导的小鼠缺氧

在小鼠中评价本发明化合物的神经保护作用。由中国科学院上海实验动物中心提供不同性别的昆明系小鼠(清洁级，证书号 005)。将重 22－28 g 的小鼠保持在 12 小时光照/黑暗周期中，使其可随意获得水和食物。将待研究的化合物溶解在 5％聚山梨酸酯 80 溶液中并在腹膜内给予剂量为 225mg/kg 的 $NaNO_2$ 之前 60 分钟口服给予此待测化合物(50mg/kg)。观察致死率，记录存活的延长。所获结果说明本发明化合物(50mg/kg，口服)

能够增加腹膜内给予 $NaNO_2$ 后的小鼠存活率。这些结果证实本发明化合物在小鼠中具有明显的抗缺氧和神经保护作用。

实施例 F: 药物组合物

制备 1000 片各含有 10mg 活性成分的片剂的配方:

(9α,13α)-1-氯-3,7-二甲氧基-17-甲基-7,8-二脱氢吗啡喃-4,6-二醇 (实施例 4).....10g

羟丙基纤维素.....2g

小麦淀粉.....10g

乳糖.....100g

硬脂酸镁.....3g

滑石.....3g

说 明 书 附 图

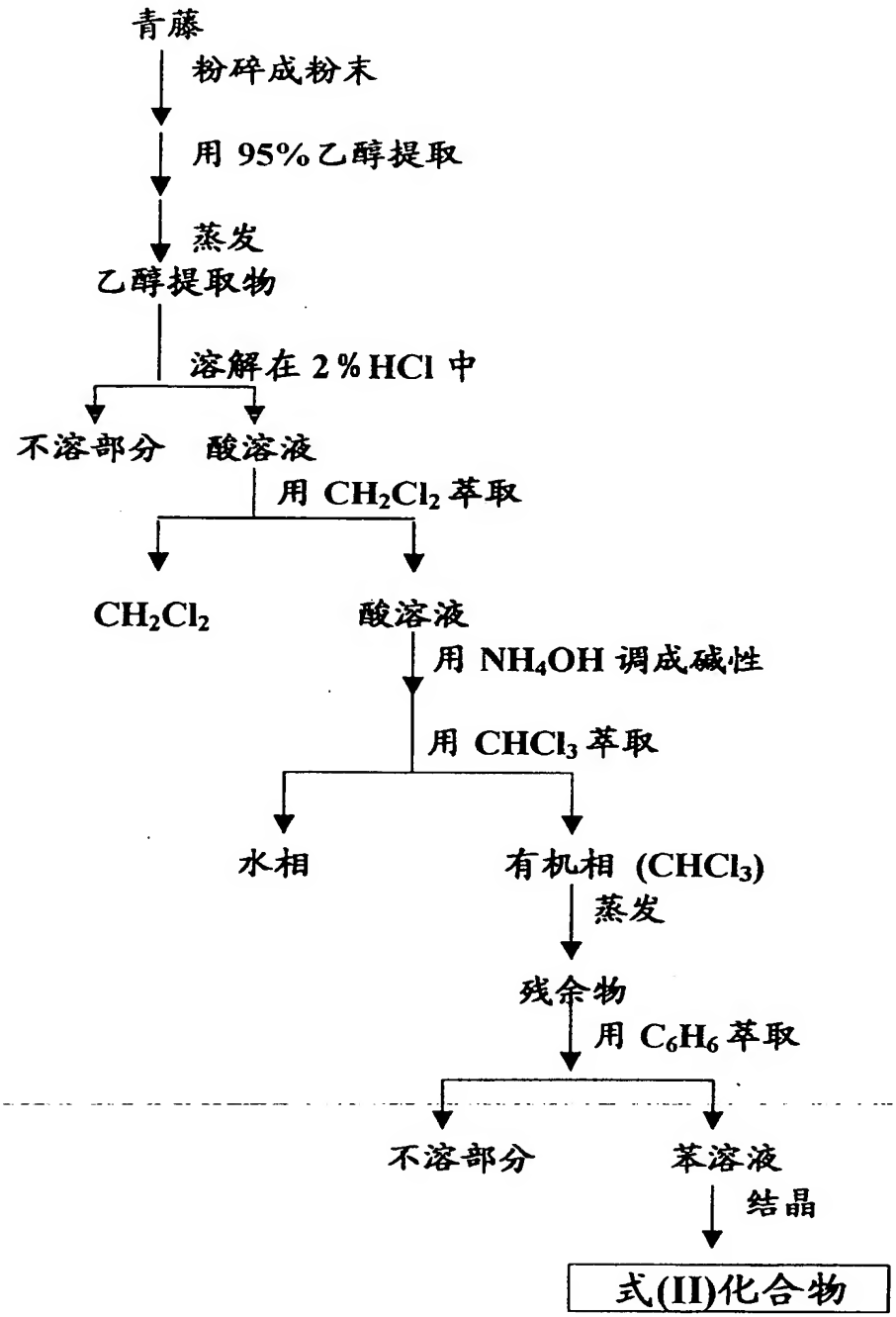


图 1: 式(II)化合物的提取